Guidance for Industry

Levothyroxine Sodium

Questions and Answers

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
February 2001
Procedural

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I. INTRODUCTION

This guidance is intended to assist sponsors who have questions about submitting new drug applications (NDAs) for orally administered levothyroxine sodium products.

On August 14, 1997, FDA announced in the *Federal Register* (62 FR 43535) that orally administered levothyroxine sodium drug products are new drugs. The notice stated that manufacturers who wish to continue to market these products must submit applications as required by section 505 of the Federal Food, Drug, and Cosmetic Act (the Act) and 21 CFR part 314 by August 14, 2000. On April 26, 2000, FDA issued a second *Federal Register* notice extending the deadline for filing applications until August 14, 2001.

The August 14, 1997, notice stated that FDA is prepared to accept new drug applications (NDAs) for these products, including section 505(b)(2) applications.[2] An applicant making a submission under section 505(b)(2) of the Act may rely on investigations described in section 505(b)(1)(A) that were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the

[1] This guidance has been prepared by the Division of Metabolic and Endocrine Drug Products and the Regulatory Policy Staff in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] The notice also stated that a bioavailability study must be completed and submitted as part of a new drug application, including a 505(b)(2) application. On June 10, 1999, FDA published in the *Federal Register* a notice of availability of a draft guidance for industry entitled *In Vivo Pharmacokinetics and Bioavailability Studies and In Vitro Dissolution Testing for Levothyroxine Sodium Tablets* to assist sponsors in conducting the bioavailability study. The final guidance is now available.

investigations were conducted. A number of questions have arisen with respect to applications for levothyroxine sodium products. This guidance is intended to answer these general questions. Sponsors should consult with the Division of Metabolic and Endocrine Drug Products for answers to specific questions.

II. REGULATORY QUESTIONS AND ANSWERS

A. Status of Marketed Products

Q: After August 14, 1997, is it permissible to begin marketing an unapproved levothyroxine sodium product that has never before been marketed?

A: No. As stated in the Federal Register notice, any levothyroxine sodium product marketed for the first time after August 14, 1997, must have an approved new drug application. Any product marketed without an approved application is an unapproved new drug and subject to enforcement action.

Q: Will FDA extend the August 14, 2000, deadline for levothyroxine sodium products to have approved applications?

A: Yes. FDA has extended the deadline to August 14, 2001.

B. Cutoff Date for 505(b)(2) Applications

Q: Will FDA approve only one NDA and convert other 505(b)(2) applications to ANDAs?

A: No. It is possible that more than one NDA will be approved. FDA will not convert any filed NDA to an ANDA.

Q: Will FDA require applications for levothyroxine sodium products to be submitted as ANDAs rather than as 505(b)(2) applications?

Yes. Until August 14, 2001, FDA will continue to accept 505(b)(2) applications. After that time, FDA will exercise its authority under section 314.101(d)(9) to refuse to file a 505(b)(2) application submitted for a levothyroxine sodium product that is pharmaceutically equivalent to an approved product. A manufacturer who wishes to submit an application for such a product should submit an ANDA. FDA believes it is in the public interest to minimize the number of nonbioequivalent levothyroxine sodium products on the market. In addition, it is an inefficient use of Agency resources to review 505(b)(2) applications for

products that are eligible for approval under the abbreviated route described in section 505(j) of the Act. Until the first NDA was approved, the ANDA route was not available because there was no listed drug to which ANDAs could refer. FDA believes that the August 14, 2001, deadline provides sufficient time for manufacturers who may have started to prepare 505(b)(2) applications before the first NDA was approved to complete and submit those applications and have them filed.

Q: After August 14, 2001, what will happen to a 505(b)(2) application that has been filed, but not yet approved? What if the application was submitted, but not filed?

A: *If the application has been filed, FDA will continue to review it. If the application has not been filed, FDA will refuse to file it.*

C. Requirements for 505(b)(2) Applications

Q: Should a 505(b)(2) application contain a patent certification?

A: *All 505(b)(2) applications are subject to the patent certification requirements at 21 CFR 314.50(i). Now that an NDA has been approved and there is a listed drug, applications that have been submitted or filed, but not yet approved, must be amended to contain a patent certification for each patent listed for the listed drug (21 CFR 314.50(i)). If there are no patents listed for the listed drug, the applicant should submit a statement, as described at 314.50(i)(1)(ii), that there are no relevant patents.*

Q: Will a 505(b)(2) application for levothyroxine sodium be assessed a user fee? If so, is it a full fee or half fee?

A: *Yes, a user fee will be assessed. The Act provides that a 505(b)(2) application is subject to an application fee if it requests approval of either (1) a molecular entity that is an active ingredient (including any salt or ester of an active ingredient) that has not been approved under section 505(b) of the Act, or (2) an indication for a use that has not been approved under section 505(b) of the Act (sections 735(1)(B) and 736(a)(1)(A)(i) of the Act). Levothyroxine sodium has been approved previously as an active ingredient in two NDAs (NDA 16-807, Thyrolar, and NDA 16-680, Euthroid). However, until recently levothyroxine sodium as a single-agent therapy was not approved for any indication. Accordingly, prior to approval of NDA 21-210 for Unithroid, a 505(b)(2) application seeking approval for levothyroxine sodium as single agent therapy for thyroid-related disorders was considered an application seeking a new indication for a use and therefore was assessed a full fee. Because an application for*

levothyroxine sodium as single agent therapy has now been approved, any application for levothyroxine sodium as single agent therapy for thyroid-related disorders submitted after August 21, 2000 (the date Unithroid was approved) will not be subject to a fee. However, a 505(b)(2) application for levothyroxine sodium seeking approval of an indication for a use different from that previously approved will be assessed a fee.

Q: Are pediatric studies necessary?

A: *As of April 1, 1999, all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, and new routes of administration must contain a pediatric assessment, unless such studies are waived or deferred (63 FR 66632; December 2, 1998).*[3] *Applications for levothyroxine sodium are subject to the pediatric rule. Applicants should discuss with the division the need for a pediatric assessment for the levothyroxine sodium product proposed in an NDA. It is possible that adequate data to support safety and effectiveness for pediatric use may be available in the scientific literature, thereby justifying a waiver.*

D. Exclusivity

Q: Was exclusivity granted to the first approved levothyroxine sodium product?

A: *No. NDA 21-210 for Unithroid did not receive exclusivity. Five-year exclusivity was not available because levothyroxine sodium has previously been approved as an active ingredient in two NDAs (NDA 16-807, Thyrolar, and NDA 16-680, Euthroid). Three-year exclusivity was not available because no new clinical investigations (other than bioavailability studies) essential to the approval of the application were conducted or sponsored by the applicant.*

E. Therapeutic Equivalence Ratings for Levothyroxine Sodium Products

Q: If the Agency approves multiple 505(b)(2) applications, how will they be rated in the Orange Book?

[3] Please refer to 21 CFR 314.55 and the preamble to the final rule (63 FR 66632, December 2, 1998) for a discussion of the grounds for waiver or deferral of the pediatric study requirement.

A: *They will be listed as BX-rated drug products for which the data are insufficient to determine therapeutic equivalence. To obtain a therapeutic equivalence rating other than BX for levothyroxine sodium tablets, an applicant should submit data comparing its product to a listed drug in* Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book).

Q: Can an NDA be supplemented with a bioequivalence study comparing the product to an approved levothyroxine sodium product?

A: *Yes. FDA would review such a study, and, if the products are bioequivalent, they would be AB-rated to each other in the Orange Book.*

F. ANDAs for Levothyroxine Sodium Products

Q: Will FDA accept ANDAs for levothyroxine sodium?

A: *Yes. Unithroid is the reference listed drug to which ANDAs should refer.*

III. SCIENTIFIC QUESTIONS AND ANSWERS

A. Stability Data

Q: How much stability data is required for an application to be acceptable for filing?

A: *FDA recommends that 6 months' long-term data and 3 months' accelerated data be included when the NDA is submitted. Additional stability data may be submitted as an amendment during the review process, and an expiration date will be granted based on the data submitted.*

B. Dissolution Method

Q: What dissolution method should applicants use?

A: *Applicants should consult with the Division of Metabolic and Endocrine Drug Products concerning dissolution testing.*

C. Overage

Q: May a stability overage be used?

A: *No.*

Q: May a manufacturing overage be used?

A. *FDA recommends consulting with the Division of Metabolic and Endocrine Drug Products before using any manufacturing overage.*